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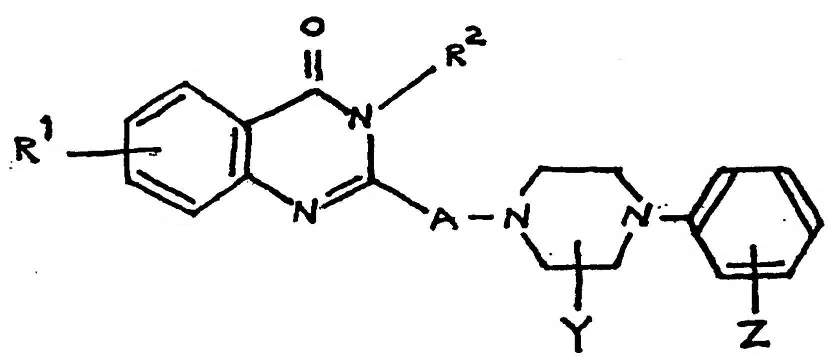
(54) PIPERAZINYL-QUINAZOLONE-(4) DERIVATIVES, PROCESS FOR PRODUCING THEM AND MEDICINES COMPRISING THEM

(71) We, BYK GULDEN LOMBERG CHEMISCHE FABRIK GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, of D-7750 Konstanz, Gottlieber Straβe 25, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to therapeutically valuable aryl-substituted piperazinylalkyl quinazolone-(4) derivatives with predominantly hypotensive properties.

For a fairly long time quinazolone-(4) derivatives have been known with sedative (Therapie, Vol. 13, (1958), pp. 30 to 45) and anticonvulsive properties (Journal of Pharmacy and Pharmacology, Vol. 12 (1960), p. 501). Of the quinazolone-(4) derivatives described in German Published Patent Application 1 231 705 and 1 249 281, 2-dimethylaminomethyl-3-methyl-6-ethoxyquinazolone-4 possesses an analgesic action which is comparable with that of the known 4-dimethylamino-1-phenyl-2,3-dimethyl-pyrazolone-5.

The present invention relates to aryl-substituted piperazinylalkyl-quinazolone-(4) derivatives of the general formula I and their salts with pharmacologically tolerable inorganic or organic acids:



In the general formula I:

R^1 signifies a hydrogen atom, a halogen atom, such as a fluorine or iodine, especially a chlorine or bromine atom, one to three straight-chained or branched, alkyl groups with 1 to 6 carbon atoms or one to three straight-chained or branched, alkoxy groups with 1 to 6 carbon atoms;

[*Price 25p*]

R^2	signifies a hydrogen atom, a straight-chained or branched, alkyl group with 1 to 6 carbon atoms, a phenyl alkyl group, in which an alkyl group contains 1 to 6 carbon atoms or a cycloalkyl group with 3 to 6 carbon atoms;
A	signifies a straight-chained or branched, alkylene group with 1 to 6 carbon atoms;
Y	signifies a hydrogen atom or an alkyl group with 1 to 4 carbon atoms and
Z	signifies a hydrogen atom or one or more alkyl, alkoxy or alkylmercapto groups each with 1 to 4 carbon atoms, trifluoromethyl groups or fluorine, chlorine or bromine atoms.

A straight-chained or branched, alkyl group with 1 to 6 carbon atoms in the radicals R^1 and R^2 is, for example, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, 1- or 2-methylbutyl, tert.-pentyl, hexyl, isohexyl 1-, 2- or 3-methylpentyl, 1-, 2- or 3-ethylbutyl, 1,2-, 1,3- or 2,3-dimethyl-butyl group.

A straight-chained or branched, alkoxy group with 1 to 6 carbon atoms in the radical R^1 is, for example, an alkoxy group derived from one of the above-mentioned alkyl groups with 1 to 6 carbon atoms, such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy, isopentyloxy, 1- or 2-methyl-butyloxy, tert.-pentyloxy, hexyloxy or isohexyloxy group.

A phenyl alkyl group in the radical R^2, in which an alkyl group contains 1 to 6 carbon atoms, is for example a benzyl or an α- or β-phenylethyl group, a cycloalkyl group in the radical R^2 with 3 to 6 carbon atoms is for example a cyclopropyl, cyclopentyl, 2- or 3-methyl-cyclopentyl or cyclohexyl group.

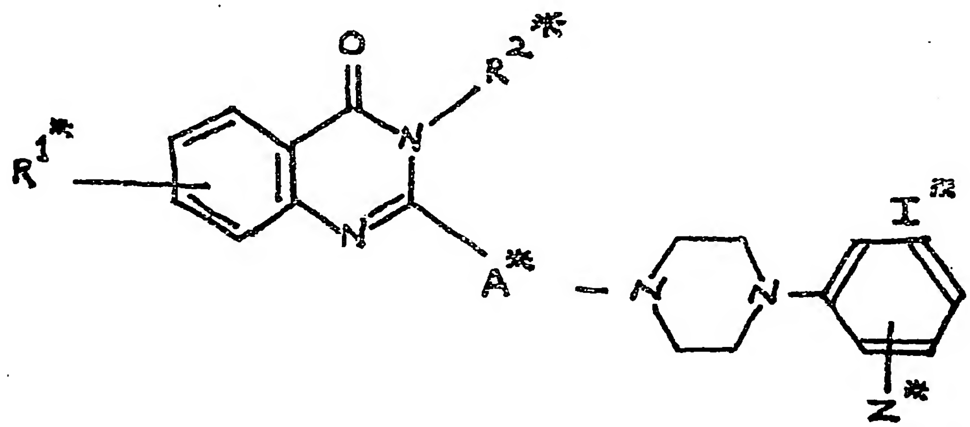
A straight-chained or branched, alkylene group A with 1 to 6 carbon atoms is, for example, a methylene, 1,1-ethylene, 1,2-ethylene, trimethylene, propylidene, 1- or 2-methylethylene, tetramethylene, 1-, 2- or 3-methyltrimethylene, butylidene, 1- or 2-ethyethylene, pentylidene, pentamethylene or hexamethylene group, and also a 1-, 2-, 3- or 4-methyltetramethylene, 1- or 2-propylethylene, 1- or 2-isopropyl-ethylene, 1-, 2- or 3-ethyl-trimethylene, 1-methyl-2-ethyl-ethylene, 2-methyl-1-ethyl-ethylene, 1,3-dimethyl-trimethylene, hexylidene, 1- or 2-butyl-ethylene, 1- or 2-isobutyl-ethylene, 1- or 2-sec.-butyl-ethylene, 1- or 2-tert.-butyl-ethylene, 1-, 2- or 3-propyltrimethylene, 1-, 2- or 3-isopropyl-trimethylene, 1-, 2-, 3- or 4-ethyl-tetramethylene, 1-, 2-, 3- or 4-ethyl-tetramethylene, 1-, 2-, 3-, 4- or 5-methyl-pentamethylene, 1,2-, 1,3-, 2,3-, 3,4- or 2,4-dimethyltetramethylene, 1-methyl-3-ethyl-trimethylene, 1,2,3-trimethyltrimethylene, 1-methyl-2-ethyltrimethylene, 3-methyl-1-ethyl-trimethylene, 2-methyl-1-ethyl-trimethylene or 2-methyl-3-ethyl-trimethylene group.

An alkyl group with 1 to 4 carbon atoms in the radicals Y and Z is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl group.

An alkoxy or alkylmercapto group in the radical Z with 1 to 4 carbon atoms is a methoxy, ethoxy, propoxy, iso-propoxy, butoxy, isobutoxy, sec.-butoxy or tert.-butoxy group or a corresponding mercapto compound, such as a methylmercapto, ethylmercapto, propylmercapto, isopropylmercapto or butylmercapto group.

The compounds according to the invention of the general formula I constitute valuable pharmaceutical products which, unlike the known compounds of a similar structure, are characterised especially by hypotensive, antihistaminic and analgesic actions. The analgesic actions correspond to those of morphine and are 30 to 40 times as great as those of the compounds described in German Patent Applications 1 231 705 and 1 249 281.

From this class of compounds, particularly good effects are possessed by aryl-substituted piperazinyl alkyl quinazolone-(4) derivatives of the general formula I* and their salts with pharmacologically compatible inorganic or organic acids,



in which

R1* signifies 1 to 2 methyl, ethyl, methoxy or ethoxy groups, especially in the 6 and/or 7 position

R2* is a hydrogen atom or a methyl or ethyl group

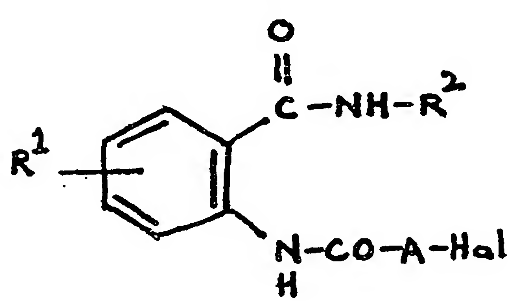
A* is an ethylene or trimethylene group

Z* is a fluorine or chlorine atom or a methyl or alkoxy group with 1 to 4 carbon atoms;

in the main 2-(2-(1-(tolyl)-piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(3-tolyl) piperzinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(4-tolyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(3-methoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(2-methoxyphenyl) piperazinyl-4)ethyl)-3-methyl-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(2-ethoxyphenyl) piperazinyl-4)-ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(2-chlorphenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(3-chlorophenyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(4-chlorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(2-fluorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(3-fluorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(4-fluorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(4-methoxyphenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(1-(2-methoxyphenyl) piperazinyl-4) methyl-6,7-dimethoxy-4(3H)-quinazolone and 2-(3-(1-(2-methoxyphenyl)-piperazinyl-4)n-propyl)-6,7-dimethoxy-4(3H)-quinazolone, especially 2-(2-(1-(2-methoxyphenyl)-piperazinyl-4)-ethyl)-6,7-dimethoxy-4(3H)-quinazolone, and also their salts with pharmacologically compatible inorganic or organic acids.

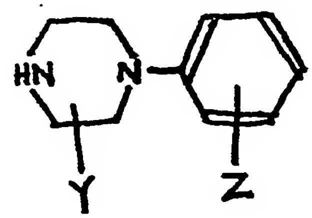
The invention also relates to a process for the production of the compounds of the general formula I, which is characterised by the fact that

a) a halogen carboxylanilide of the general formula II,



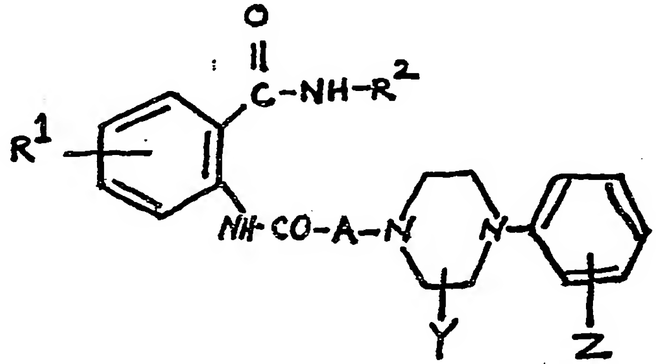
II

in which R¹, R² and A have the meanings above and Hal signifies a halogen atom — preferably a chlorine or bromine atom — is reacted with an aryl piperazine of the general formula III,



III

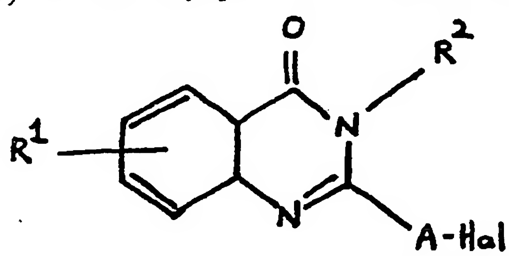
in which Y and Z have the meanings given above, and the compound of the general formula IV



IV

so obtained in which R¹, R², A, Y and Z have the meanings given above, is intramolecularly condensed at elevated temperature or

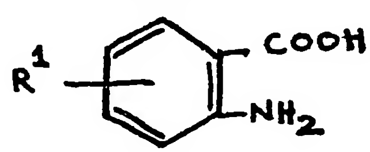
b) an ω-halo-alkyl quinazolone of the general formula V,



V

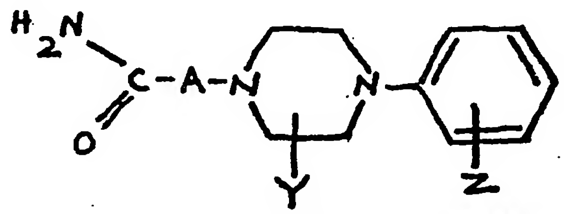
in which R¹, R², A and Hal have the meanings given above, is reacted with an aryl piperazine of the general formula III or

c) an anthranilic acid of the general formula VI

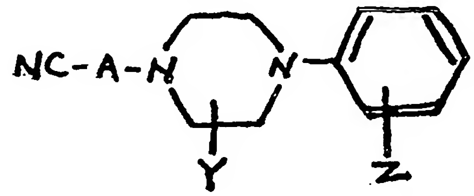


VI

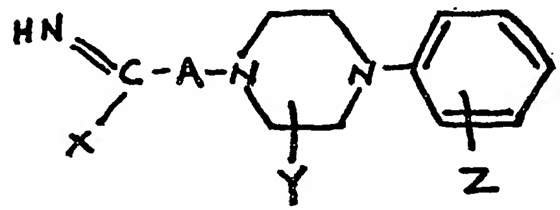
in which R¹ has the meaning given above, or a reactive ester of such a compound is reacted with a compound of the general formula VII, VIII or IX



VII



VIII

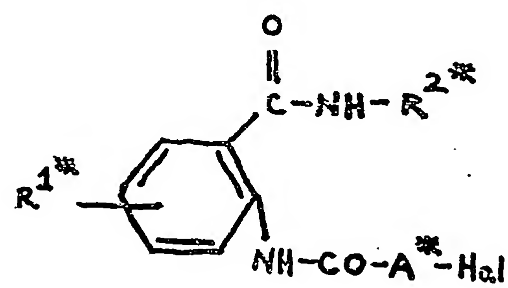


IX

in which A, Y and Z have the meanings given above and X is an amino group or an alkoxy group with 1 to 4 carbon atoms, at elevated temperature, and, if desired, the radical R^2 is introduced into the compound so obtained by alkylation, and if desired the compounds obtained according to a), b) and c) are converted into the salts of pharmacologically compatible inorganic or organic acids or a salt obtained is converted into the free compound.

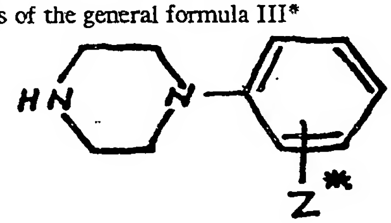
Preferably one reacts

a) compounds of the general formula II*



II*

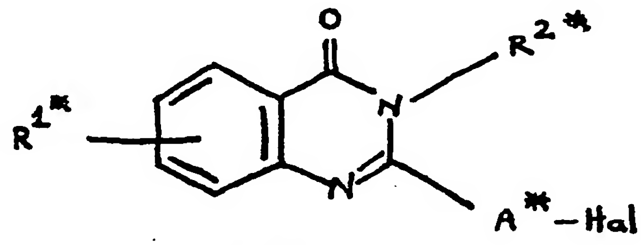
with aryl piperazines of the general formula III*



III*

in which R^{1*}, R^{2*}, A* and Z* and Hal have the meanings given above,

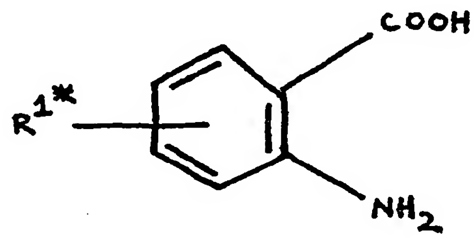
b) an ω-halogen alkyl quinazolone of the general formula V*



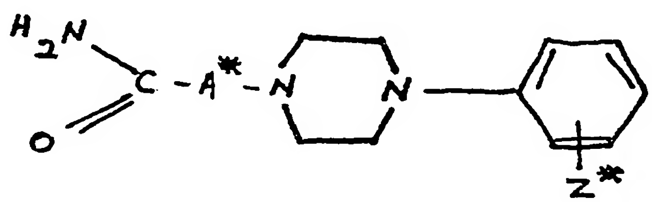
V*

in which R^{1*}, R^{2*} and A* have the meanings given above, is reacted with an aryl piperazine of the general formula III*, or

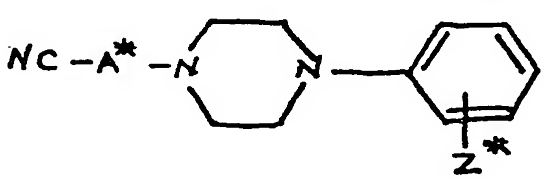
c) an anthranilic acid of the general formula VI*



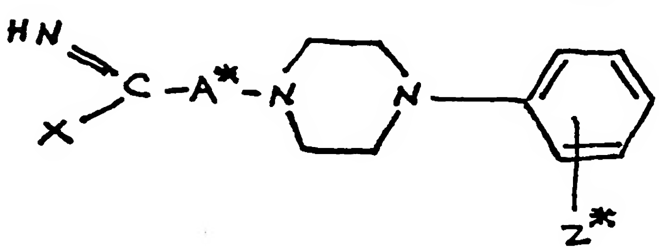
or a reactive ester of such a compound, is reacted with a compound of the general formula VII*, VIII* or IX*



VII*



VIII*



IX*

and if desired one introduces the radical R^{2*}, R^{1*}, R^{2*}, A^* and Z^* and X having the meanings given above.

The first stage of the process according to a), the reaction of the compounds of the general formula II with aryl piperazines of the general formula III, is carried out possibly in the presence of an inert organic solvent, for example of an alcohol such as ethyl alcohol, or isopropyl alcohol, ketone such as acetone, or methylethylketone, strongly polar fatty acid amide or nitrile such as dimethylformamide, dimethylacetamide, or acetonitrile or mixtures thereof, at temperatures between 50 and 120°C, especially between 50 and 70°C. In such cases it is advantageous to use an equivalent quantity of auxiliary base such as triethylamine, ethyldicyclohexylamine, dicyclohexylamine or potassium carbonate or to carry out the reaction with at least double the equivalent quantity of aryl piperazine in or without the solvents mentioned above.

As halogencarboxylanilides of the general formula II one can use, for example: the 2-carbamyl anilides of chloracetic, bromacetic or iodoacetic acid of 2- or 3-(chloro- or bromo-) propionic acid, of 2-, 3- or 4-(chloro or bromo-) butyric acid, of 2-, 3-, 4- or 5-(chloro- or bromo-) valeric acid, of 2-, 3-, 4-, 5- or 6-(chloro- or bromo-) caproic acid, of 2-, 3-, 4-, 5-, 6- or 7-(chloro- or bromo)- oenanthic acid, of 2-methyl-3-(chloro or bromo-) butyric acid, of 2-ethyl-4-(chloro- or bromo-) butyric acid, of 3-ethyl-4-(chloro- or bromo-) butyric acid, the 4- or 5- methyl - 2 - carbamyl anilides, the 4- or 5 - ethyl - 2 - carbamyl anilides, the 4- or 5 - propyl - 2-carbamyl anilides, the 4,5-dimethyl or 4,5,6-trimethyl-2-carbamyl anilides, the 4- or 5-(chloro- or bromo-)-2-carbamyl anilides, the 4- or 5-(methoxy, ethoxy-, propoxy, isopropoxy-, butoxy-, isobutoxy-, sec.-butoxy-, or tert.-butoxy-)-2-carbamyl anilides, the 4,5- or 5,6-(dimethoxy- or diethoxy)-)-2-carbamyl-anilides, the 4,5,6-trimethoxy-2-carbamyl anilides or the 2-(N-methylcarbamyl, N-ethylcarbamyl, N-propylcarbamyl, N-isopropylcarbamyl, N-butylcarbamyl, N-pentylcarbamyl, N-isopentylcarbamyl, N-benzylcarbamyl, N-(β-phenylethyl)-carbamyl, N-cyclopropylcarbamyl, N-cyclopentyl-carbamyl or N-cyclohexylcarbamyl)-4,5-dimethoxy anilides of the acids mentioned above.

Halogencarboxylanilides which are preferably used are those of the general formula II*, for example the 2-(carbamyl, N-methylcarbamyl or N-ethylcarbamyl)-4- or 5-(methyl- or ethyl-) anilides, the 2-(carbamyl, N-methylcarbamyl or N-ethyl-carbamyl-)-4- or 5-(methoxy- or ethoxy)-anilides or the 2-(carbamyl, N-methylcarb-amyl or N-ethylcarbamyl)-4,5-dimethoxy- or diethoxy)-anilides of 3-(chloro- or bromo)-propionic acid or of 4-(chloro- or bromo)-butyric acid.

As aryl piperazines of the general formula III, one may use for example: 1-phenylpiperazine, 1-(o-, m- or p-tolyl) piperazine, 1-(2-, 3- or 4-(ethyl-, propyl, isopropyl-, butyl-, isobutyl-, sec.-butyl- or tert.-butyl)-phenyl)-piperazine, 1-(2-, 3- or 4-(methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, sec.-butoxy- or tert.-butoxy)-phenyl)piperazine, 1-(2-, 3- or 4-(methylmercapto-, ethylmercapto-, propyl-mercapto-, isopropylmercapto-, butylmercapto-, isobutylmercapto-, sec.-butylmercapto- or tert.-butyl-mercapto)-phenyl) piperazine, 1-(2-, 3- or 4-trifluoromethylphenyl)-piper-azine, 1-(2-, 3- or 4-(fluoro-, chloro- or bromo)-phenyl) piperazine, 1-phenyl-(2 or 3)-methyl-piperazine, 1-phenyl-(2 or 3)-ethylpiperazine, 1-phenyl-(2 or 3)-propylpiper-azine, or 1-phenyl-(2 or 3)-butylpiperazine, and also 1-(o-, m- or p-tolyl)-2-methyl-piperazine, 1-(o-, m- or p-tolyl)-3- propylpiperazine, 1-(2-ethylphenyl)-3-butylpiper-azine, 1-(3-propylphenyl)-2-isopropylpiperazine, 1-(2-methoxyphenyl)-(2 or 3)- methyl-piperazine, 1-(2-, 3- or 4-ethylmercaptophenyl)-3-ethylpiperazine, 1-(2-trifluoromethyl-phenyl)-3-isobutypiperazine or 1-(2-, 3- or 4-chlorophenyl)-2-methylpiperazine.

Preference is given to aryl piperazines of the formula III*, for example 1-(o-, m- or p-tolyl)-piperazine, 1-(3- or 4-methoxyphenyl)-piperazine, 1-(2-, 3- or 4-(ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, sec.-butoxy- or tert.-butoxy)-phenyl)-piper-azine or 1-(2-, 3- or 4-(fluoro or chloro)-phenyl) piperazine, especially 1-(2-methoxy-phenyl)-piperazine.

The intramolecular condensation according to the second stage of the process a) takes place either by heating a compound of the general formula IV, preferably to 100 to 120°C, with strongly basic agents, such as alkali metal hydroxides, alkali metal alcoholates, tetra-alkyl ammonium hydroxides, or with an excess of the aryl piperazine used in the first stage of the process according to a), and if desired an organic solvent is used, such as ethylene glycol monomethyl ether, monoethyl ether or dimethylform-amide. The condensation can also be carried out by heating to above the melting point, preferably to temperatures between 150 and 250°C, in vacuo or in a high-boiling inert organic liquid, such as diphenylmethane or diphenylether.

The replacement of the halogen atom of a compound of the general formula V

by an aryl piperazine of the general formula III according to the process b) is advantageously carried out under the conditions stated for the first stage of the process a).

As ω-halogenalkyl quinazolones of the general formula V one can use, for example, the following:
2-(chloro-, bromo- or iodo-methyl)-4-(3H)-quinazolone, 2-(1- or 2-(chloro- or bromo)-ethyl)-4(3H)-quinazolone, 2-(1-, 2- or 3-(chloro- or bromo)-propyl)-4-(3H)-quinazolone, 2-(1-, 2-, 3- or 4-(chloro- or bromo-)butyl)-4-(3H)-quinazolone, 2-(1-, 2-, 3-, 4- or 5-(chloro- or bromo) pentyl-4-(3H)-quinazolone, 2-(1-, 2-, 3-, 4-, 5- or 6- (chloro- or bromo)-hexyl)-4-(3H)quinazolone, 2-(1- or 2-methyl-3-chloropropyl)-4(3H)-quinazolone, 2-(1- or 2-ethyl-3-chloropropyl)-4(3H)-quinazolone, or the 6- or 7- (methyl-, ethyl-, propyl-, isopropyl-, butyl-, tert.-butyl- or hexyl)-, the 6,7- or 7,8-dimethyl-, the 6-methyl-7-propyl-, the 6,7,8-trimethyl-, the 6- or 7-(chloro- or bromo)-, the 6- or 7-(methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, sec.-butoxy- or tert.-butoxy-, the 6,7- or 7,8-(dimethoxy- or diethoxy)- or the 6,7,8-trimethoxy-4(3H)-quinazolones with the radicals mentioned in position 2 of the above compounds, or the 6- or 7-(methyl-, ethyl-, propyl-, isopropyl-, tert.-butyl- or hexyl)-, the 6,7- or 7,8-dimethyl-, the 6-methyl-7-propyl-, the 6,7,8-trimethyl-, the 6- or 7-(chloro- or bromo)-, the 6- or 7-(methoxy-, ethoxy-, propoxy-, isopropoxy, butoxy-, isobutoxy-, sec.-butoxy-, or tert.-butoxy), the 6,7- or 7,8-(dimethoxy- or diethoxy)- or the 6,7,8,-trimethoxy-3-(methyl-, ethyl-, propyl-, isopropyl-, butyl-, pentyl-, isopentyl-, benzyl-, β-phenylethyl-, cyclopropyl-, cyclopentyl- or cyclohexyl)-4-(3H)-quinazolones with the radicals mentioned in position 2 of the above compounds. Preference is given to ω-halogenalkyl quinazolones of the general formula V*, for example 2-(2-chloro- or bromo)- ethyl-tert.-butoxy-, the 6,7- or 7,8-(dimethoxy- or diethoxy)- or the 6,7,8-trimethoxy-4(3H)-quinazolones, 2-(2-(chloro- or bromo)-ethyl- or 3-(chloro or bromo)propyl)-3-(methyl- or ethyl)-6- or 7-(methyl-, ethyl-, methoxy- or ethoxy)-4(3H)-quinazolones, 2-(2-(chloro- or bromo)-ethyl- or 3-(chloro- or bromo)-propyl)-6,7- or 7,8-dimethyl-, dimethoxy- or diethoxy)-4(3H)-quinazolones or 2-(2-chloro- or bromo)- ethyl- or 3-(chloro- or bromo)-propyl-3-(methyl- or ethyl) 6,7- or 7,8-dimethyl-, dimethoxy- or diethoxy)-4(3H)-quinazolones.

The condensation according to the process c) is carried out by heating the initial substances to temperatures between 60 and 180°C, preferably 120 to 180°C when using amides or nitriles and preferably 60 to 120°C when using imide acid esters or amidines, possibly in a solvent, for example a low-molecular alcohol, and advantageously at its boiling point.

The anthranilic acids of the general formula VI which can be used are, for example, anthranilic acid; 4- or 5-monoalkylanthranilic acids, such as, 4- or 5-(methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, sec.-butyl-, tert.-butyl-, pentyl-, isopentyl- or hexyl-, anthranilic acid; 3,4- or 4,5-dialkylanthranilic acids, such as 3,4- or 4,5-(dimethyl-, diethyl-, dipropyl-, ethylmethyl- or butylmethyl)-anthranilic acid; 3,4,5-trialkylanthranilic acids, such as 3,4,5-trimethyl- or triethylanthranilic acid, 4- or 5-halogen-anthranilic acids, especially 4- or 5-chloroanthranilic acid or 4- or 5- bromo-anthranilic acid; 4- or 5-(methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy- sec.-butoxy-, tert.-butoxy, pentyloxy-, isopentyloxy- or hexyloxy-anthranilic acid; 3,4- or 4,5-dialkoxy- anthranilic acids, such as for example 3,4- or 4,5-(dimethoxy-, diethoxy-, dipropoxy-, ethoxy-hexyloxy-, butoxy-methoxy- or methoxy-isopropoxy)-anthranilic acid; or 3,4,5-trialkoxy-anthranilic acids, such as for example 3,4,5-trimethoxy- or triethoxy-anthranilic acid.

Preference is given to anthranilic acids of the general formula VI*, for example 4- or 5-(methyl-, ethyl-, methoxy- or ethoxy)-anthranilic acid or 3,4- or 4,5-(dimethyl-, diethyl-, dimethoxy- or diethoxy)-anthranilic acid. A reactive ester of a compound of the general formula VI or VI* is, for example, the ester of a lower alkanol with 1 to 4 carbon atoms, especially the methyl- or ethyl-ester, of one of the above-mentioned anthranilic acids. (4-arylpiperazinyl-(1))-carboxylamides, nitriles, amidines and imino-esters of the general formulae VI, VIII or IX are, for example, 4-aryl-piperazinyl-(1)-acetamide, -acetonitrile, acetamidine or -acetiminoethyl ester, 2- or 3-(4-aryl-piperazinyl-(1))-propionamide, -propionitrile, -propionamidine or -propionic acid imino-methyl- or ethyl ester, 2-, 3- or 4-(4-aryl-piperazinyl-(1))-butyramide, -butyronitrile, -butyramidine or -butyric acid iminomethyl- or ethyl ester, 2-, 3-, 4- or 5-(4-aryl-piperazinyl-(1))-valero-amide, -valeronitrile, -valeroamidine or -valeric acid imino-methyl ester, 2-, 3-, 4-, 5- or 6-(4-aryl-piperazinyl-(1))-capronamide, -capronitrile, -capronamidine, or -caproic acid iminoethyl ester, 2-, 3-, 4-, 5-, 6- or 7-(4-arylpiperazinyl)-(1))-oenanthamide, -oenanthonitrile, -oenanthamidine or oenanthic acid imino-

methyl ester, 2-methyl-3-(4-aryl-piperazinyl-(1))-butyramide, -butyronitrile, -butyramidine or -butyric acid iminomethyl ester, in which the aryl piperazinyl radical represents the radical of one of the aryl piperazines mentioned above for formula III.

Preferably the reaction is carried out with compounds of the formulae VII* VIII* or IX*, for example 3-(4-aryl piperazinyl-(1))-propionamide, -propionitrile, -propionamidine, -propionic acid iminomethyl- or ethyl ester and 4-(4-aryl-piperazinyl-(1))-butyramide, -butyronitrile, -butyramidine, -butyric acid iminomethyl- or ethyl ester, in which the aryl piperazinyl radical represents the radical of one of the aryl piperazines mentioned above for formula III*.

The production of salts of non-toxic inorganic and organic acids can usually be carried out by dissolving the free bases and adding the requisite quantity of acid. Examples of inorganic acids which may be considered are: hydrogen halide acids such as hydrochloric acid or hydrobromic acid, also sulphuric acid, phosphoric acid or sulphamic acid. By way of example one may mention as organic acids: acetic acid, propionic acid, lactic acid, glycolic acid, gluconic acid, oxalic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, acetylglycine, benzoic acid, salicylic acid, pamoic acid, methanesulphonic acid, β-hydroxy-ethanesulphonic acid, polygalacturonic acid, polyvinylcarboxylic acid or ethylenediamine tetracetic acid. The salts of the compounds according to the invention can be readily soluble or sparingly soluble in water, the sparingly soluble salts being used particularly for the production of delayed action forms of the compounds according to the invention.

Surprisingly the compounds according to the invention of general formula I possess only slight sedative properties and no anticonvulsive properties, but pronounced hypotensive, antihistaminic and analgesic properties. The following tables I to V show the extent of these activities as well as details of toxicity and compare them with the effects of known substances. Substances used for comparison were: phentolamine, chlorodiazepoxide, Meprobamate, aminophenazone, morphine hydrochloride, piprine hydrate = (1-methyl-piperidyl-4)-benzhydryl ether -8-chlorotheophyillinate.

TABLE I

Influence on the blood pressure and cardiac frequency and also on the carotid sinus reflex of the narcotised cat

Product of Example No.	Blood pressure lowered by		Cardiac frequency		Inhibition of the carotid sinus reflex by	
	30% by	50% by	lowered	raised	30% by	50% by
2	0.029	>1.6	+	−	<0.01	0.02
6	0.07	0.61	+	−	0.12	0.35
10	0.03	1.4	+	−	<0.02	0.03
11	0.04	>1.6	+	−	0.017	0.04
14	0.9	>1.6	±	±	0.04	0.15
17	4.5	>4.5	+	−	—	—
Phentolamine	0.1	0.7	−	+	0.1	0.5

Table I provides a general summary of the influence of different piperazinylquinazolones on the blood pressure, the cardiac frequency and the carotid sinus reflex of the narcotised cat.

TABLE II

Influence on the blood pressure and the cardiac frequency of the narcotised rat and also on the hypertensive effect of 0.001 mg/kg i/v l-adrenalin and noradrenalin on the despinalised rat

Product of Example	LD_{50} (mean lethal dose) on the mouse	Narcotised rat			Despinalised rat 50% inhibition of hypertensive effect after i/v dose	
		Blood pressure lowered by 30% by mg/kg i/v	Cardiac frequency		Adrenalin by mg/kg i/v	Noradrenalin by mg/kg i/v
			lowered	increased		
1	70	0.3	+	–	0.23	5.0
2	70	0.65	–	–	0.042	1.4
3	200	0.32	–	–	0.35	5.0
4	100	0.65	+	–	—	—
6	600	0.35	+	–	0.036	>2.5
8	350	0.12	+	–	0.035	—
10	300	0.4	+	–	0.0085	1.8
11	200	0.1	+	–	0.048	>2.5
14	150	0.18	+	–	0.058	>2.5
15	200	0.2	+	–	0.32	4.3
16	300	0.6	+	–	0.57	4.0
20	300	0.65	+	–	0.05	1.15
Phentolamine	200	0.63	–	–	0.047	0.18

Table II shows the influence of various piperazinyl quinazolones on the blood pressure and the cardiac frequency of the narcosed rat and also on the hypertensive effect of 0.001 mg/kg i.v. 1-adrenaline and noradrenaline on the despinalised rat. The mean lethal doses for the mouse are also given.

From Tables I and II it can be seen that the piperazinyl quinazolones according to the invention generally have a stronger hypotensive action and a lower toxicity than phentolamine which in the blood vessels specifically inhibits the stimulating action of noradrenaline and adrenaline.

The inhibition of the carotid sinus reflex brought about by the piperazinyl quinazolones occurs at lower doses than the spontaneous lowering of the blood pressure in the cat. This shows that the compounds according to the invention inhibit central hypertensive mechanisms of the circulation.

The central damping actions of the piperazinyl quinazolones on the mouse can be seen from Table III. A comparison between the doses which influence the circulation and those which have a central damping effect shows that the influence on the circulation takes place preferentially, which means to say that the hypotensive doses are below those which reduce the motor behaviour, that is to say the normal movement operation.

Key to Table III:

a = dose at which 50% of the mice fall from a rotating bar;

b = dose at which an average of 50% of the mice display the following symptoms: inhibition of spontaneous motility, sedation, muscular relaxation, loss of power to grip and hold themselves on a horizontal wire mesh;

c = average percentage inhibition of the running activity of mice which had been pre-treated with 5 mg/kg. of α-amphetamine sulphate (reckoned on the activity of mice which had only received α-amphetamine sulphate) over a period of 180 minutes;

d = percentage prolongation of the duration of sleep of mice which had received 75 mg/kg. of hexobarbital, reckoned on the duration of the sleep of control animals.

TABLE III

Central effects on the mouse

Product of Example No.	a PD_{50}mg/kg i.p.	b SP_{50}mg/kg oral	c % inhibition of motility in the treadwheel by 12mg/kg i/p	25mg/kg i/p	d % prolongation of sleep under hexobarbital by 15 mg/kg i.p.
1	33	1000	15	55	64
2	35	140	11	10	121
3	24	60	13	41	69
4	23	70	51	65	125
6	34	40	19	28	79
11	53	110	18	32	87
12	34	500	0	19	78
13	46	200	+15	+15	44
14	61	180	+16	1	68
16	14	65	10	49	103
18		1000	+22	+12	±>15
Chlordiazepoxide	38	8	+15	19	324
Meprobamate	95	300	+11	+28	18

From Table IV below one can see the analgesic action, measured in terms of the delayed reaction during the thermal irritation of the mouse tail. The analgesically effective doses are also below those which reduce the motor behaviour, that is to say the normal movement processes (cf. Table III).

TABLE IV

Product of Example No.	Analgesic effect on the mouse Delay in the defence reaction after the thermal stimulation of the tail of the mouse by 25% by mg/kg per os
1	1.5
2	1
3	2
4	3
5	<1
6	1.5
7	1
8	10
10	2
11	4
12	1.5
13	2
14	2
15	1
16	2.5
17	2
18	8
20	2
Aminophenazone	80
Morphine hydrochloride	2

Another surprising feature is the strong antihistamine activity of the piperazinyl-quinazolones according to the invention:

TABLE V

Product of Example No.	Antihistaminic action 50% inhibition of the histamine spasm of the isolated guinea pig small intestine by g/ml.
1	3.5×10^{-9}
2	6.5×10^{-9}
3	1.5×10^{-9}
4	8×10^{-9}
6	3×10^{-9}
7	2×10^{-9}
11	3×10^{-9}
12	3.5×10^{-10}
13	2.5×10^{-9}
15	7×10^{-9}
16	3.5×10^{-9}
20	2.5×10^{-9}
Piprine hydrinate	1.5×10^{-8}

An orientating clinical test which was carried out with the compound of Example 6 on 7 female and 1 male patient with doses of 10 and 20 mg per os, showed a very good tolerance, no effect on the sensorium and a statistically significant lowering of the systolic and diastolic blood pressure. Figs 1 and 2 show the variations in the blood pressure at various doses of 2-(2-(1-(2-methoxyphenyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in relation to the mean initial blood pressure of 171.9 mm Hg systolic and 95.3 mm Hg diastolic; Fig. 1 is based on the mean initial blood pressure of 171.9 mm Hg systolic and Fig. 2 is based on the mean initial blood pressure of 95.3 mm Hg diastolic. The lowering of the blood pressure is therefore seen to be dependent upon the dose. The difference in the action of 10 and 20 mg. is statistically confirmed.

From the pharmacological and clinical investigations it can be seen that the piperazinyl quinazolones of the general formula I and their salts with pharmacologically tolerable inorganic or organic acids are valuable therapeutic aids, particularly for the treatment of high blood pressure.

Pharmaceutical products can be prepared which contain one or more of the compounds according to the invention in the form of the free bases or of a pharmacologically tolerable acid addition salt as active principle, possibly also in admixture with other pharmacologically active substances. These pharmaceutical products can be produced in the usual manner by combining the active principle with a pharmaceutical support, such as a filler, a diluent, a corrective and/or other usual ingredients for pharmaceutical products. The products can be produced in the solid state in the form of tablets or capsules or in the liquid state in the form of solutions or suspensions. In the case of administration by intravenous route three times a day the individual dose is from 1 to 50 mg, preferably 5 to 20 mg. For administration three times a day by intramuscular route the individual dose is 1 to 50 mg., preferably 10 to 25 mg. When administered per os three times a day, the individual dose is from

1 to 100 mg., preferably 5 to 60 mg. The pharmaceutical products according to the invention can also be administered in other ways, for example by intraperitoneal or subcutaneous route. The pharmaceutical support can also contain the usual diluents or tabletting additives, such as cellulose powder, corn starch, lactose and talcum, just as are usual for such purposes.

The invention therefore also relates to pharmaceutical products, especially for the treatment of high blood pressure, which are characterised by their containing one or more compounds of the general formula I.

Example of a batch for the production of 75,000 tablets containing 20 mg. of active principle of Example 6

Ingredients:

1.500 kg.	compound of Example 6
6.000 kg.	corn starch
4.875 kg.	lactose
0.225 kg.	amorphous silica
0.300 kg.	sodium lauryl sulphate
0.375 kg.	polyvinylpyrrolidone
1.200 kg.	pectin
0.375 kg.	talcum
0.150 kg.	magnesium stearate
15.000 kg.	

The active principle, the corn starch, the lactose, the amorphous silica and the sodium lauryl sulphate are mixed and sieved. This mixture is moistened with a solution of the polyvinylpyrrolidone in 2.4 litres of alcohol and granulated through a sieve with a mesh of 1.25 mm. The granulate is dried at 40°C and mixed with the pectin, talcum and magnesium stearate. This mixture is pressed on the rotary press into tablets of 200 mg. and a diameter of 8 mm.

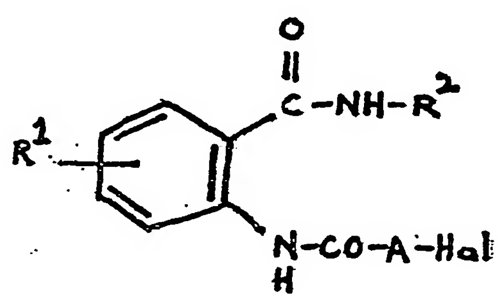
Example of a batch for the production of 200,000 capsules containing 20 mg. active principle

Ingredients:

4.000 kg.	compound of Example 6
15.990 kg.	microcrystalline cellulose
0.010 kg.	amorphous silica
20.000 kg.	

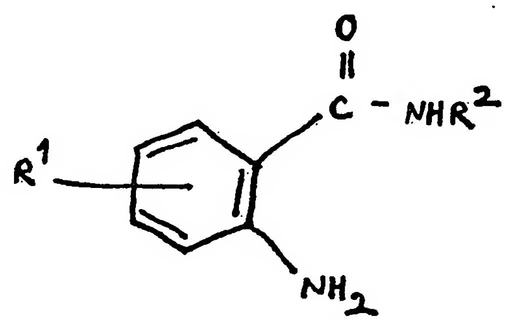
The compound of Example 6 in the finely powdered form, the microcrystalline cellulose and the unpressed amorphous silica are thoroughly mixed and filled into hard gelatin capsules of size 4.

Finally the invention relates to a process for the production of halogenalkanoic acid-6-carbamyl anilides of the general formula II



II

in which R^1, R^2, A and Hal have the meanings given above used as starting materials for the production of the amyl - substituted piperazinyl alkyl quinazolone - (4) derivatives having the general formula (I); the process is characterised by the fact that 6-carbamyl anilines of the general formula X:



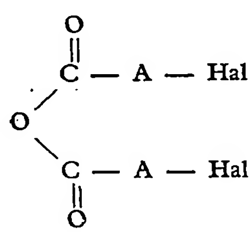
X

in which R¹ and R² have the meanings given above, are reacted with halogenalkanoic acid halides of the general formula XI

$$Hal' - \overset{\overset{\displaystyle O}{\|}}{C} - A - Hal$$

XI

in which Hal and A have the meanings given above and Hal′ signifies a chlorine or bromine atom, or halogenalkanoic acid anhydrides of the general formula XII



XII

in which A and Hal have the meanings given above, in the presence of one or more inorganic and/or organic auxiliary bases in an inert organic solvent.

In the process for the production of halogenalkanoic acid -6-carbamyl anilides of the general formula II or II* one uses as inorganic auxiliary bases alkali or alkaline earth metal carbonates, especially sodium carbonate or potassium carbonate, or alkali metal bicarbonates, especially sodium bicarbonate; preferred auxiliary organic bases are tertiary amines, for example triethylamine, ethyldisopropylamine, pyridine. As organic auxiliary bases it is also possible to use an excess of 6-carbamyl aniline of the general formula II or II*. As inert solvent one uses preferably hydrocarbons, for example, benzene, toluene or xylene, halogenated hydrocarbons, for example methylene chloride, chloroform, trichlorethylene, chlorobenzene or o-dichlorobenzene, or ethers, for example di-isopropyl ether, tetrahydrofuran or dioxan, or mixtures of the above-mentioned solvents.

The reaction temperatures are not critical; they are generally within the range from 0 to 80°C, especially 10 to 30°C.

In order to obtain good yields one proceeds as follows in a particularly preferred form of execution of the process of the invention for the production of halogenalkanoic acid-6-carbamyl anilides of the general formula II or II*:

The 6-carbamyl aniline is placed in one of the above-mentioned solvents. Per mole of 6-carbamyl aniline one adds 0.5 moles of halogenalkanoic acid halide or anhydride, dissolved in one of the solvents listed above, accompanied by stirring and if necessary by cooling. To the resultant reaction mixture one adds, per mole of 6-carbamyl aniline used, 0.5 moles of organic auxiliary base, accompanied by stirring. One adds further haloalkanoic acid halide or anhydride, namely 0.25 moles per mole of 6-carbamyl aniline used, that is to say one-half of the quantity previously added. This

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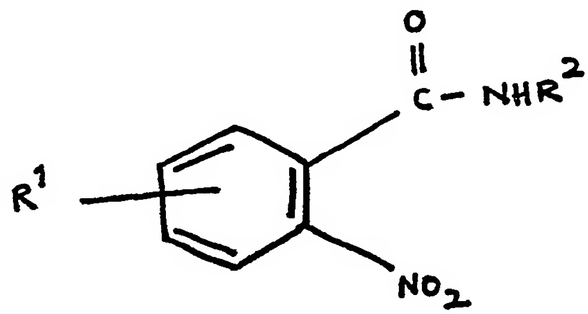
is followed once again by the addition of 0.25 moles of organic auxiliary base per mole of 6-carbamyl aniline used, that is to say one-half of the quantity previously added. This alternating addition of half the quantities of haloalkanoic acid halide or anhydride and half the quantities of organic auxiliary base is repeated again several times. The isolation of the haloalkanoic acid-6-carbamyl anilides of the general formula II or II* is carried out in the usual manner, for example by the addition of dilute acid followed by filtration or extraction.

The 6-carbamyl anilines used as initial compounds in the process according to the invention for the production of halogenalkanoic acid-6-carbamyl anilines can be produced by the catalytic reduction of o-nitrobenzoic acid amides of the general formula XIII

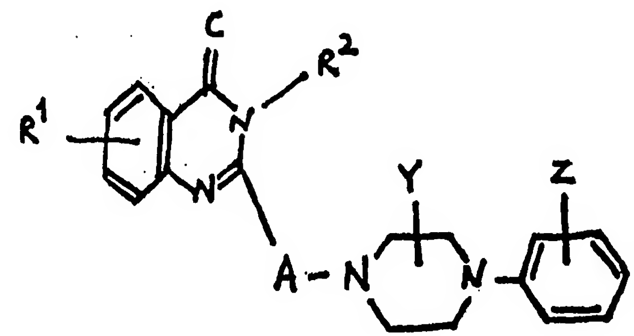


XIII

in which R^1 and R^2 have the meanings given above. The o-nitrobenzoic acid amides can in turn be obtained by reacting the corresponding o-nitrobenzoic acid chlorides with primary amines or ammonia.

The examples are intended to illustrate the invention in greater detail without restricting same.

TABLE VI



Example No.	R^1	R^3	A	Y	Z	M.P. °C.	Crystallised from	Yield % of theory
1	6.7-di-OCH_3	H	—CH_2—CH_2—	H	H	214—215	Ethyl acetate	78
2	6.7-di-OCH_3	H	—CH_2—CH_2—	H	2-CH_3	204—205	Ethyl acetate	64
3	6.7-di-OCH_3	H	—CH_2—CH_2—	H	3-CH_3	212—213	Ethyl acetate	86
4	6.7-di-OCH_3	H	—CH_2—CH_2—	H	4-CH_3	232—233	Ethyl acetate	52
5	6.7-di-OCH_3	H	—CH_2—CH_2—	H	3-CF_3	239—240	Ethyl acetate	74
6	6.7-di-OCH_3	H	—CH_2—CH_2—	H	2-OCH_3	214—215	Ethyl alcohol	75
7	6.7-di-OCH_3	H	—CH_2—CH_2—	H	3-OCH_3	194—196	Ethyl acetate	57
8	6.7-di-OCH_3	CH_3	—CH_2—CH_2—	H	2-OCH_3	211—212	Ethyl acetate	46
9	6.7-di-OCH_3	—CH_2—CH_2—C_6H_5	—CH_2—CH_2—	H	2-OCH_3	162—163	Ethyl acetate	42

TABLE VI (Continued)

Example No.	R^1	R^2	A	Y	Z	M.P. °C	Crystallised from	Yield % of theory
10	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	2-OC_2H_5	207—208	Ethanol	62
11	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	2-Cl	226—227	Ethyl acetate	81
12	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	3-Cl	224—225	Ethyl acetate	60
13	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	4-Cl	231—232	Ethyl acetate	68
14	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	2-F	210	Ethyl acetate	56
15	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	3-F	221	Ethyl acetate	64
16	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	4-F	250—251	Ethyl acetate	45
17	6.7-di-OCH_3	H	$—CH_2—CH_2—$	H	4-OCH_3	218	Ethanol	52
18	6.7-di-OCH_3	H	$—CH_2—$	H	2-OCH_3	210	Ethyl acetate	83
19	H	H	$—CH(C_2H_5)—$	H	2-OCH_3	180—181	Ethyl acetate/ Methanol 9:1	83,5
20	6.7-di-OCH_3	H	$—CH_2—CH_2—CH_2—$	H	2-OCH_3	175—176	Methanol	59
21	6.7-di-OCH_3	Cyclohexyl	$—CH_2—CH_2—CH_2—$	H	2-OCH_3	214—216	Ethyl acetate	22,5
22	6.7-di-OCH_3	$—CH_2—CH_2—CH(CH_2)_2$	$—CH_2—$	H	2-OCH_3	147	Ethyl acetate/ Cycloh. 3:7	37
23	6.7.8-tri-OCH_3	H	$—CH_2—CH_2—$	H	2-OCH_3	164	Ethyl acetate	82
24	6.7.8-tri-OCH_3	H	$—CH_2—CH_2—$	H	2-Cl	172	Ethyl acetate	85

Example 1

2-(2-(1-phenylpiperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone

To a solution of 14.2 g (0.04 moles) of 3-bromopropionic acid-(3,4-dimethoxy-6-carbamyl) anilide in 100 mls. of acetonitrile heated to 50°C one adds a mixture of 7g (0.04 moles) of 1-phenylpiperazine and 7.8 g (0.04 moles) of dicyclohexylamine in 50 mls. of ethyl alcohol. The crystal paste which is immediately formed is stirred for about 5 hours at 50 to 70°C and then freed from solvents in vacuo. The residue is taken up in 100 mls. of hot chloroform, separated from the undissolved residue and the clear solution is concentrated by evaporation in vacuo. The oily product is dissolved in 100 mls. of ethylene glycol monoethyl ether, 2.24 g (0.04 moles) of solid potassium hydroxide are added and the mixture is heated to 100°C for 10 to 15 minutes. Whilst stirring vigorously the solution is poured into 500 mls. of iced water which contains 3 g of ammonium chloride and semi-concentrated aqueous ammonia is added until the reaction is alkaline. The precipitate is filtered at the pump, washed thoroughly with water and dried. After re-crystallisation from ethyl acetate, one obtains 15 g (78% of theory) of 2-(2-(1-phenylpiperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 214—215°C.

In the same way as described in Example 1, the following compounds are produced by using the corresponding initial material:

Example 2

2-(2-(1-(2-tolyl)-piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 64% and with a melting point of 204—205°C.

Example 3

2-(2-(1-(3-tolyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 86% and with a melting point of 212—213°C.

Example 4

2-(2-(1-(4-tolyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 52% and with a melting point of 232—233°C.

Example 5

2-(2-(1-(3-trifluoromethylphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone with a yield of 74% and with a melting point of 239—240°C.

Example 6

2-(2-(1-(2-methoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 75% and with a melting point of 214—215°C.

Example 7

2-(2-(1-(3-methoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 57% and with a melting point of 195—196°C.

Example 8

1-(2-(1-(2-methoxyphenyl)piperazinyl-4)ethyl)-3-methyl-6,7-dimethoxy-4(3H)-quinazolone in a yield of 46% and with a melting point of 211—212°C.

Example 9

2 - (2 - (1 - (2 - -methoxyphenyl)piperazinyl - 4)ethyl) - 3 - phenethyl - 6,7 - dimethoxy-4(3H)-quinazolone in a yield of 42% and with a melting point of 162—163°C.

Example 10

2-(2-(1-(2-ethoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 62% and with a melting point of 207—208°C.

Example 11

2-(2-(1-(2-chlorophenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(2H)-quinazolone in a yield of 81% and with a melting point of 26—227°C.

Example 12

2-(2-(1-(3-chlorophenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a ... 1 of 60% and with a melting point of 224—255°C.

Example 13

2-(2-(1-(4-chlorophenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 68% and with a melting point of 231—232°C.

Example 14

2-(2-(1-(2-fluorophenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 56% and with a melting point of 210°C.

Example 15

2-(2-(1-(3-fluorophenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 64% and with a melting point of 221°C.

Example 16

2-(2-(1-(4-fluorophenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone in a yield of 45% and with a melting point of 250—251°C.

Example 17

2-(2-(1-(4-methoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone

One dissolves 10 g (0.032 moles) of 3-bromopropionic acid-(3,4-dimethoxy-6-carbamyl)-anilide in 50 mls. of dimethylformamide, adds a solution of 9.1 g (0.036 moles) of 1-(4-methoxyphenyl)piperazine and 7.5 g (0.036 moles) of ethyldicyclohexylamine in 50 mls. of dimethylformamide and the solution is stirred at 80°C for 2 hours. The ethyldicyclohexylamine hydrobromide formed is filtered off at the pump and washed thoroughly with dimethylformamide. The combined filtrates are mixed with 50 mls. of 2N caustic soda solution heated to 100—110°C for 10 to 15 minutes and finally poured into 500 mls. of ice-cooled ammonium chloride solution. The crystalline precipitate which separates out is filtered off at the pump, thoroughly washed with water and dried in vacuo. The crude product is purified by crystallisation from ethyl alcohol using a hot extractor and in this way one obtains 7.1 g (52% of the theory) of 2-(2-(1-(4-methoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 218°C.

Example 18

2-(1-(2-methoxyphenyl)piperazinyl-4)methyl-6,7-dimethoxy-4(3H)-quinazolone

A mixture of 21.0 g (0.077 moles) of chloracetic acid-(3,4-dimethoxy-6-carbamyl)-anilide and 44.3 g (0.23 moles) of 1-(2-methoxyphenyl)piperazine is heated whilst stirring to 110°C. The mass which solidifies after 10 minutes is dissolved in 100 mls. of acetonitrile and stirred for a further 30 minutes at 70°C. The mixture is freed from solvent in vacuo, the residue is taken up in 100 mls. of ethylene glycol monomethyl ether which contains 5.6 g of potassium hydroxide, and heated to 100°C for 15 minutes. The solution is poured on to ice, 20 mls. of saturated ammonium chloride solution are added and semi-concentrated aqueous ammonia until the reaction becomes slightly alkaline. The precipitate is filtered at the pump, washed with water and dried in vacuo. Any adhering impurities are removed by briefly boiling the crude product with ethyl acetate and then filtering again and drying. In this way one obtains 26.2 g (83% of theory) of 2-(1-(2-methoxyphenyl)piperazinyl-4)-methyl-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 210°C.

Example 19

2-(α-(1-(2-methoxyphenyl)piperazinyl-4)-n-propyl)-4(3H)-quinazolone

19.2 g (0.06 moles) of 2-(2-bromobutyrylamino)-benzamide and 35.7 g (0.186 moles) of 1-(2-methoxyphenyl)piperazine are heated to 70°C for 2 hours whilst stirring, and then mixed with a solution of 6.4 g of potassium hydroxide in 70 mls. of glycol monoethyl ether and then heated to 70°C for a further 30 minutes. The reaction mixture is distributed between saturated ammonium chloride solution and chloroform, the chloroform phase is separated and after drying over calcined potassium carbonate is concentrated by evaporation in vacuo. The oily residue is boiled up with ethyl acetate, allowed to cool slowly and the crystal mass is filtered off at the pump. By redissolving in a 9:1 mixture of ethyl acetate and methyl alcohol it is possible to purify the crude product. In this way one obtains 21.3 g (83.5% of theory) of 2-(α-(1-(2-methoxyphenyl)-piperazinyl-4)-n-propyl)-4(3H)-quinazolone with a melting point of 180—181°C.

Example 20

By using corresponding initial materials, one obtains by the mode of operation stated in Example 19 2-(3-(1-(2-methoxyphenyl)-piperazinyl-4)-n-propyl)-6,7-di-

methoxy-4(3H)-quinazolone in a yield of 59% and with a melting point of 175—176°C.

Example 21

2-(3-(1-(2-methoxyphenyl)piperazinyl-4)-n-propyl)-3-cyclohexyl-6,7-dimethoxy-4(3H)-quinazolone

10.0 g (0.023 moles) of 4-(bromobutyric acid-(3,4-dimethoxy-6-cyclohexylcarbamyl) anilide and 22.0 g (0.115 moles) of 1-(2-methoxyphenyl) piperazine are stirred at 120°C for 4 hours. The reaction mixture is then poured into 100 mls. of saturated ammonium chloride solution and extracted with chloroform. After drying the chloroform extracts over calcined potassium carbonate, they are concentrated by preparation in vacuo. The residual dark brown oil is purified by column chromatography over silica gel neutral (0.05—0.2 mm) using chloroform as eluent. The eluate is concentrated in vacuo and the residue is heated at 0.5 mm Hg for 2 hours at 160°C. Then the crude product is recrystallised from ethyl acetate. In this way one obtains 2.6 g (22.5% of theory) of 2-(3-(1-(2-methoxyphenyl) piperazinyl-4)-n-propyl)-3-cyclohexyl-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 214—216°C.

Example 22

2-(1-(2-methoxyphenyl) piperazinyl-4) methyl-3-isoamyl-6,7-dimethoxy-4(3H)-quinazolone

4.0 g (0.011 moles) of chloroacetic acid-(3,4-dimethoxy-6-isoamylcarbamyl) anilide and 4.3 g (0.022 moles) of 1-(2-methoxyphenyl) piperazine are stirred in 20 mls. of dimethylformamide for 3 hours at 70°C, the solvent is removed for the most part in vacuo, the residue is distributed between 2 N caustic soda solution and chloroform and finally the chloroform phase is purified by column chromatography over 100 g silica gel neutral (0.05—0.2 mm) using chloroform as eluent. The eluate is concentrated in vacuo, the residue is heated in 50 mls. of dimethylformamide with 5 mls. of a 40% solution of benzyltrimethyl ammonium hydroxide in methyl alcohol for 30 minutes at 100°C and the reaction mixture is then poured into 500 mls. of saturated ammonium chloride solution. The oily reaction product is extracted with chloroform, after drying the chloroform phase and concentration in vacuo it is isolated and made to crystallise with a 3:7 mixture of ethyl acetate and cyclohexane. In this way one obtains 2.0 g (37% of theory) of 2-(1-(2-methoxyphenyl)-piperazinyl-4)-methyl-3-isoamyl-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 147°C.

Example 23

By using the corresponding initial compounds, by preceding analogously to Example 2 one obtains 2-(2-(1-(2-methoxyphenyl)-piperazinyl-4)-ethyl)-6,7,8-trimethoxy-4(3H)-quinazolone with a yield of 82% and a melting point of 164°C.

Example 24

By using the corresponding initial compounds, by proceeding analogously to Example 22 one obtains 2-(2-(1-(2-chlorophenyl)-piperazinyl-4)-ethyl)-6,7,8-trimethoxy-4(3H)-quinazolone with a yield of 85% and a melting point of 172°C.

Example 25

58.1 g (0.3 moles) of 4,5-dimethoxy-anthranilic acid and 118.35 g (0.45 moles) of 3-(4-(2-methoxyphenyl)-piperazinyl-1)-propionamide are heated to 150°C for 7 hours. After cooling, the mixture is heated with 2N aqueous sodium carbonate solution, extracted with methylene chloride and the methylene chloride solution separated is shaken four times with 0.1 N aqueous sodium hydroxide solution. The caustic soda extract is clarified with active carbon, mixed with hydrochloric acid until the precipitate which is initially formed is redissolved and then rendered alkaline with 2N aqueous sodium carbonate solution, when the quinazolone is precipitated. After recrystallisation from ethyl alcohol one obtains 2-(2-(1-(2-methoxyphenyl)-piperazinyl-4)-ethyl)-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 214—215°C.

By using the corresponding initial compounds it is possible by means of the process described here to obtain the piperazinylalkyl-4(3H)-quinazolones described in Examples 1 to 7, 10 to 20, 23 and 24.

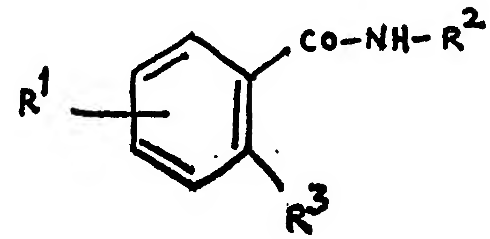
Example 26

40.1 g (0.1 moles) of imino ethyl 3-(4-(2-methoxyphenyl)-piperazinyl-1) propionate trihydrochloride are placed in a mixture of 100 g of 40% aqueous potassium carbonate solution and 100 mls. of ether cooled to $-10°C$. The ether solution is separated after being shaken, dried with potassium carbonate and the ether distilled off. The oily residue is poured into a hot solution of 2.5 g (0.1 moles) of ethyl 4,5-dimethoxy-anthranilate in 100 mls. of ethyl alcohol and heated under a reflux for 1.5 hours. After removing a part of the ethyl alcohol the reaction mixture is poured into water and the precipitated reaction product is purified by hot extraction with ethyl acetate. One obtains 2-(2-(1-(2-methoxyphenyl)-piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone with a melting point of 214—215°C.

By using the corresponding initial materials and the methods of operation described here one can obtain the piperazinyl-alkyl-4(3H)-quinazolones described in Examples 1 to 7, 10 to 20, 23 and 24.

TABLE VII

Precursors and Intermediates



R^1	R^2	R^3	M.P. °C	Crystallised from	Yield % of theory
3,4-di-OCH_3	CH_3	NO_2	188—189	Ethyl acetate	97
3,4-di-OCH_3	—$(CH_2)_2$—C_6H_5	NO_2	156—157	Isopropanol	74
3,4-di-OCH_3	—$(CH_2)_2$—$CH(CH_3)_2$	NO_2	141—142	Ethyl acetate	73
3,4-di-OCH_3	Cyclohexyl	NO_2	189—190	Ethyl acetate	71
3,4-di-OCH_3	CH_3	NH_2	138—139	Ethyl alcohol	77
3,4-di-OCH_3	—$(CH_2)_2$—C_6H_5	NH_2	116—117	Ethyl acetate	83
3,4-di-OCH_3	—$(CH_2)_2$—$CH(CH_2)_2$	NH_2	98—98,5	Isopropanol	68,5
3,4-di-OCH_3	Cyclohexyl	NH_2	147—148	Water	81,5

TABLE VII (Continued)

Precursors and Intermediates

No. of Example	R^1	R^2	R^3	M.P. °C	Crystallised from	Yield % of theory
27	H	H	NH—CO—CH—CH$_2$—CH$_3$ | Br	146	Benzene	72
28	3,4-di-OCH$_3$	H	NH—CO—CH$_2$—Cl	218	Ethyl acetate	75
29	3,4-di-OCH$_3$	—(CH$_2$)$_2$—CH(CH$_3$)$_2$	NH—CO—CH$_2$—Cl	142	Isopropanol/ Cyclohex. 1 : 1	34
30	3,4-di-OCH$_3$	H	NH—CO—CH$_2$—CH$_2$—Br	188	Ethyl acetate	75
31	3,4-di-OCH$_3$	CH$_3$	NH—CO—CH$_2$—CH$_2$—Br	150—151	Ethyl acetate	71
32	3,4-di-OCH$_3$	—(CH$_2$)$_2$—C$_6$H$_5$	NH—CO—CH$_2$—CH$_2$—Br	153—154	Ethyl acetate	75
33	3,4-di-OCH$_3$	H	NH—CO—CH$_2$—CH$_2$—CH$_2$—Cl	165—166	Ethyl acetate	63
34	3,4-di-OCH$_3$	Cyclohexyl	NH—CO—CH$_2$—CH$_2$—CH$_2$—Br	174—175	Chloroform	89

The initial compounds used in the following Examples 27 to 34 can be produced according to or similarly to the following process:

6-nitroveratrumic acid-N-methylamide

To a solution of 15 g (0.67 moles) of methylamine in 300 mls. of methyl alcohol one adds slowly, whist stirring and cooling, a solution of 50 g (0.21 moles) of 6-nitro-veratrumic chloride (C.A. Fletscher and M.T. Bogert, J. org. Chem. *4*, 71 (1939)) in 600 mls. of benzene and the reaction mixture is stirred for 30 minutes at room temperature. The mixture is poured into two litres of iced water, the crystal mass is filtered at the pump and after drying in vacuo is purified if desired by crystallisation from ethyl acetate. In this way one obtains 47.0 g (97% of theory) of 6-nitroveratrumic acid-N-methylamide with a melting point of 188—189°C.

1331522 COMPLETE SPECIFICATION

1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

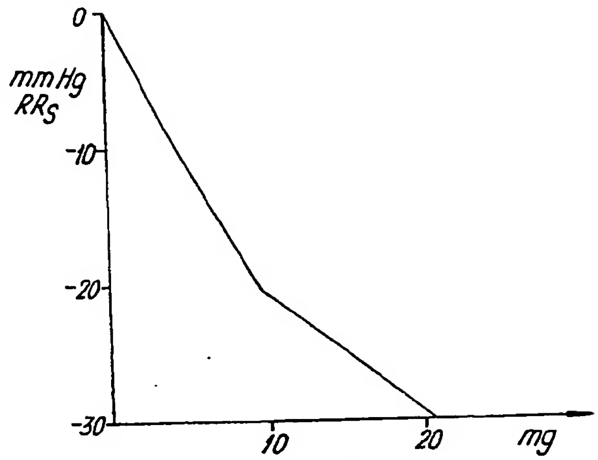


Fig. 1.

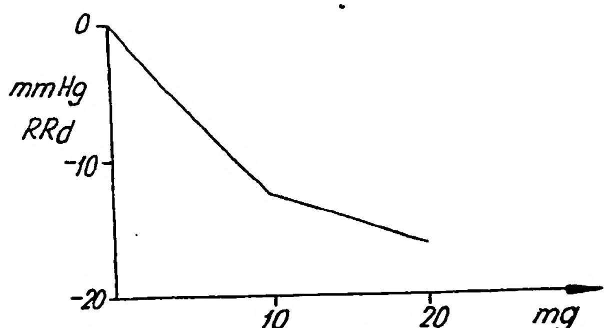


Fig. 2.

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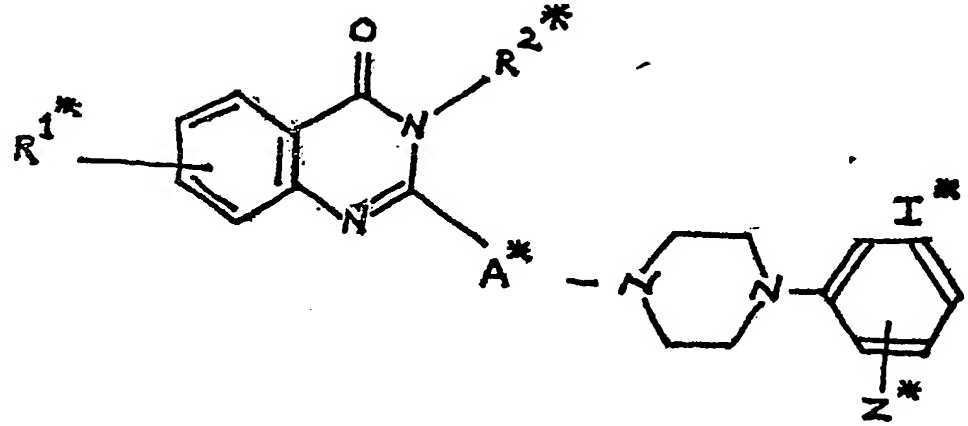
I* and their salts with pharmacologically compatible inorganic or organic acids,



in which R¹*, R²*, A* and Z* are as defined in Claim 3.

25. Process in accordance with Claims 22 or 23, characterised by the fact that 2-(2-(1-(2-tolyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone, 2-(2-(1-(3-tolyl)-piperazinyl - 4)ethyl) - 6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2 - (1 - (4 - tolyl)-piperazinyl - 4)ethyl) - 6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2 - (1 - (3-methoxyphenyl)piperazinyl - 4)ethyl) - 6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2-(1 - (2 - methoxyphenyl)piperazinyl - 4)ethyl - 3 - methyl - 6,7 - dimethoxy - 4(3H)-quinazolone, 2 - (2 - (1 - (2 - ethoxyphenyl)piperazinyl - 4)ethyl) - 6,7 - dimethoxy-4(3H) - quinazolone, 2 - (2 - (1 - (2 - chlorophenyl)piperazinyl - 4)ethyl) - 6,7 - di-methoxy - (4(3H) - quinazolone, 2 - (2 - (1 - (3 - chlorophenyl)piperazinyl - 4)ethyl)-6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2 - (1 - (4 - chlorophenyl)piperazinyl-4)ethyl) - 6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2 - (1 - (2 - fluorophenyl)-piperazinyl - 4)ethyl) - 6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2 - (1 - (3-fluorophenyl)piperazinyl - 4)ethyl) - 6,7 - dimethoxy - 4(3H) - quinazolone, 2 - (2-(1 - (4 - fluorophenyl)piperazinyl - 4)ethyl - 6,7 - dimethoxy - 4(3H) - quinazolone, 2-(2 - (1 - (4 - methoxyphenyl)piperazinyl - 4)ethyl) - 6,7 - dimethoxy - 4(3H) - quina-zolone, 2 - (1 - (2 - methoxyphenyl)piperazinyl - 4)methyl - 6,7 - dimethoxy - 4(3H)-quinazolone or 2 - (3 - (1 - (2 - methoxyphenyl) - piperazinyl - 4) - n - propyl) - 6,7-dimethoxy - 4(3H) - quinazolone, and also their salts with pharmacologically com-patible inorganic or organic acids are produced.

26. Process in accordance with one of claims 22 or 23, characterised by the fact that one produces 2-(2-(1-(2-methoxyphenyl)piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazoline and also its salt with pharmacologically compatible inorganic or organic acids.

27. A process for the preparation of an aryl-substituted piperazinylalkyl-quinazol-one-(4) derivative of formula I substantially as described with reference to any one of Examples 1 to 27.

28. A pharmaceutical preparation comprising one or more aryl-substituted piperazinylalkyl-quinazolone-(4) derivatives according to claim 1 or a pharmacologic-ally compatible inorganic or organic salt thereof in admixture with one or more solid or liquid pharmaceutically acceptable inert carriers.

29. A pharmaceutical preparation in accordance with claim 28, characterised by the fact that the dose unit for intravenous administration contains 1 to 50 mg., for intramuscular administration 1 to 50 mg., and for oral administration 1 to 100 mg., of one or more of the compounds according to claim 1.

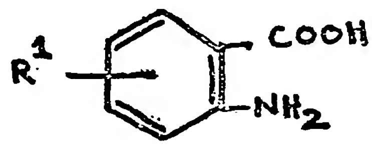
30. A pharmaceutical preparation according to claim 28 containing one or more of the compounds according to Claim 3.

31. A pharmaceutical preparation according to claim 28 containing one or more of the compounds named in Claims 5 to 19.

32. A pharmaceutical preparation according to claim 28 containing 2-(2-(1-(2-methoxyphenyl)piperazinyl-4)-ethyl)-6,7-dimethoxy-4(3H)-quinazolone.

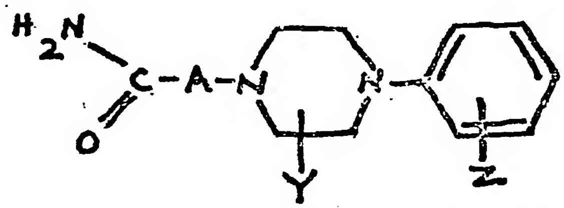
in which R^1, R^2, A and Hal have the meanings given above, is reacted with an aryl-piperazine of the general formula III, or

c) an anthranilic acid of the general formula VI

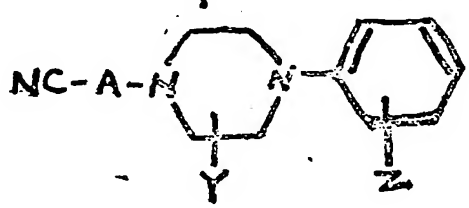


VI

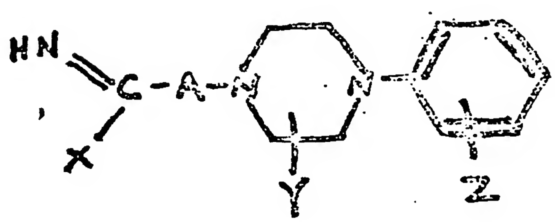
in which R^1 has the meaning given above, or a reactive ester of such a compound is reacted with a compound of the general formulae VII, VIII or IX,



VII



VIII



IX

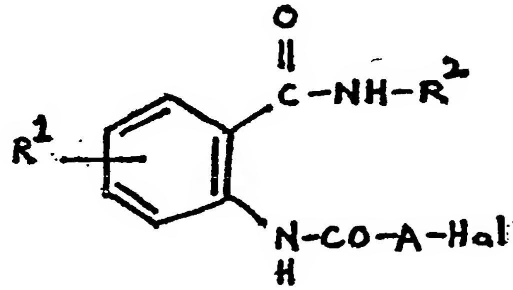
in which A, Y and Z have the meanings given above, and X signifies an amino group or an alkoxy group with 1 to 4 carbon atoms, at elevated temperature and the radical R^2 is introduced into the compound so obtained by alkylation, and if desired the compounds obtained according to a), b) and c) are converted with pharmacologically compatible inorganic or organic acids into the salts or a salt obtained is converted into the free base.

23. Process in accordance with Claim 22, characterised by the fact that in the variant a) a compound of the general formula II is used, in which a halogen atom is a chlorine or bromine atom.

24. Process in accordance with one of Claims 22 or 23, characterised by the fact that aryl-substituted piperazinylalkyl quinazolone-(4) derivatives of the general formula

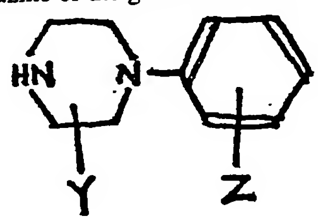
in which R^1, R^2, A, Y and Z are as defined in claim 1, characterised by the fact that

a) a compound of the general formula II



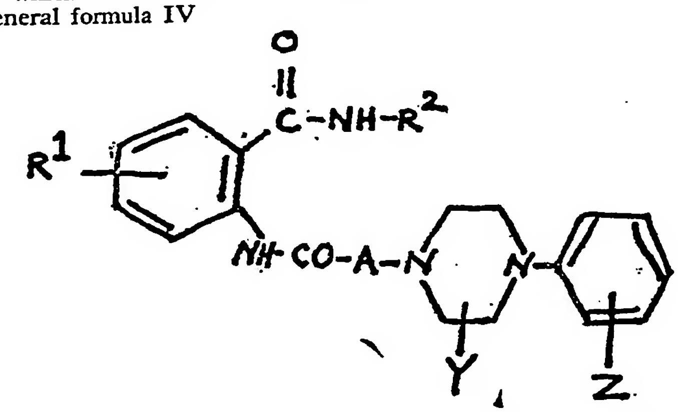
II

in which R^1, R^2 and A have the meanings given above, and Hal siginfies a halogen atom, is reacted with an arylpiperazine of the general formula III,



III

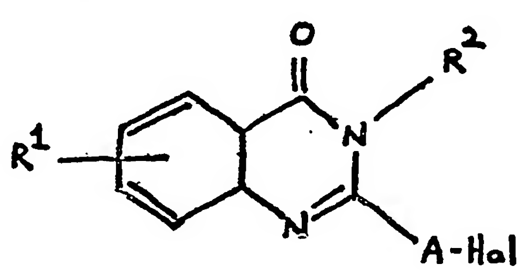
in which Y and Z have the meanings given above, and the compound obtained of the general formula IV



IV

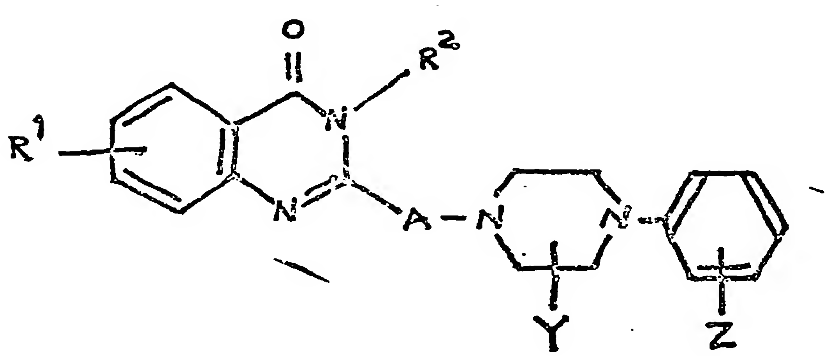
in which R^1, R^2, A, Y and Z have the meanings given above, is intramolecularly condensed at elevated temperature, or

b) an ω-haloalkylquinazolone of the general formula V



V

5. 2-(2-(1-(2-tolyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
6. 2-(2-(1-(3-tolyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
7. 2-(2-(1-(4-tolyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
8. 2-(2-(1-(3-methoxyphenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
9. 2-(2-(1-(2-methoxyphenyl) piperazinyl-4)ethyl)-3-methyl-6,7-dimethoxy-4(3H)-quinazolone.
10. 2-(2-(1-(2-ethoxyphenyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4) (3H)-quinazolone.
11. 2-(2-(1-(2-chlorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
12. 2-(2-(1-(3-chlorophenyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
13. 2-(2-(1-(4-chlorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
14. 2-(2-(1-(2-fluorophenyl) piperazinyl-4) ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
15. 2-(2-(1-(3-fluorophenyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
16. 2-(2-(1-(4-fluorophenyl)piperazinyl-4)ethyl-6,7-dimethoxy-4(3H)-quinazolone.
17. 2-(2-(1-(4-methoxyphenyl) piperazinyl-4)ethyl)-6,7-dimethoxy-4(3H)-quinazolone.
18. 2-(1-(2-methoxyphenyl) piperazinyl) -4)methyl-6,7-dimethoxy-4(3H)-quinazolone.
19. 2-(3-(1-(2-methoxyphenyl)-piperazinyl - 4) - n-propyl)-6,7-dimethoxy-4(3H)-quinazolone.
20. 2-(2-(1-(2-methoxyphenyl)piperazinyl - 4)ethyl) - 6,7-dimethoxy-4(3H)-quinazolone.
21. The aryl-substituted piperzinylalkyl-quinazolone-(4) compounds of formula I described in Examples 1 to 25.
22. Process for the production of aryl-substituted piperazinylalkyl-quinazolone-(4) derivatives of the general formula I and their salts of pharmacologically compatible inorganic or organic acids,



I

3,4-dimethoxy-6-aminobenzoic acid-N-methylamide

To a solution of 15.8 g (0.06 moles) of 6-nitroveratrumic acid-N-methylamide in 200 mls. of methyl alcohol boiling under a reflux one adds 15 mls. of an approximately 50% aqueous suspension of Raney nickel and then while stirring adds drop by drop slowly 16.1 g (0.3 moles) of hydrazine hydrate. As soon as the reaction which takes place with considerable frothing has ended, the catalyst is filtered off, the filtrate is evaporated to dryness in vacuo and the residue is re-dissolved in ethyl alcohol. In this way one obtains 10.6 g (76.8% of theory) of 3,4-dimethoxy-6-aminobenzoic acid-N-methylamide with a melting point of 138—139°C.

Example 27

2-bromobutyric acid-(2-carbamyl) anilide

To a solution of 15.0 g (0.11 moles) of anthranilamide in 200 mls. of dioxane there are first of all added drop by drop, accompanied by thorough stirring, a solution of 11.3 g (0.55 moles) of 2-bromobutyryl chloride in 25 mls. of dioxane and then a solution of 5.55 g (0.55 moles) of triethylamine in 25 mls. of dioxane. Into the resultant reaction mixture there is added slowly drop by drop 5.65 g of 2-bromobutyryl chloride in 12.5 mls. of dioxane and then a solution of 2.78 g of triethylamine in 12.5 mls. of dioxane, that is to say one-half quantities of the previously combined reactants. This alternating addition of half quantities of 2-bromobutyryl chloride and half quantities of triethylamine is repeated a further twice. After the addition is terminated, the reaction mixture is stirred at room temperature for a further 30 minutes and then freed for the most part from solvent in vacuo. The residue is mixed up into a suspension in 0.5 litres of 0.5N hydrochloric acid, filtered at the pump and washed neutral with water and dilute soda solution. After drying in vacuo and crystallisation from benzene, one obtains 24.2 g (72% of theory) of 2-bromobutyric acid-(2-carbamyl)-anilide with a melting point of 146°C. From the benzene solution it is possible to recover a further 6.0 g, the total yield being increased to 90% of theory.

In an analogous manner the following are produced:

Example 28

Chloracetic acid-(3,4-dimethoxy-6-carbamyl) anilide in a yield of 75% of theory and with a melting point of 218°C.

Example 29

Chloracetic acid-(3,4-dimethoxy-6-(N-isoamylcarbamyl) anilide in a yield of 34% of theory and with a melting point of 142°C.

Example 30

3-bromopropionic acid-(3,4-dimethoxy-6-carbamyl) anilide in a yield of 75% of theory and with a melting point of 188°C.

Example 31

3-bromopropionic acid-(3,4-dimethoxy-6-(N-methylcarbamyl) anilide in a yield of 71% of theory with a melting point of 150—151°C.

Example 32

3-bromopropionic acid-(3,4-dimethoxy-6-(N-β-phenylethylcarbamyl)) anilide in a yield of 75% of theory and with a melting point of 153—154°C.

Example 33

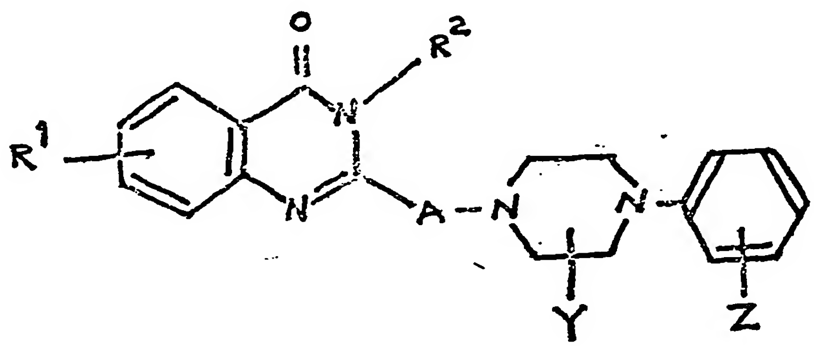
4-chlorobutyric acid-(3,4-dimethoxy-6-carbamyl) anilide in a yield of 63% of theory and with a melting point of 165—166°C.

Example 34

4-bromobutyric acid-(3,4-dimethoxy-6-(N-cyclohexylcarbamyl))-anilide in a yield of 89% of theory and with a melting point of 174—175°C.

WHAT WE CLAIM IS:—

1. Aryl-substituted piperazinylalkyl-quinazolone-(4) derivatives of the general formula I and their salts with pharmacologically tolerable inorganic or organic acids,

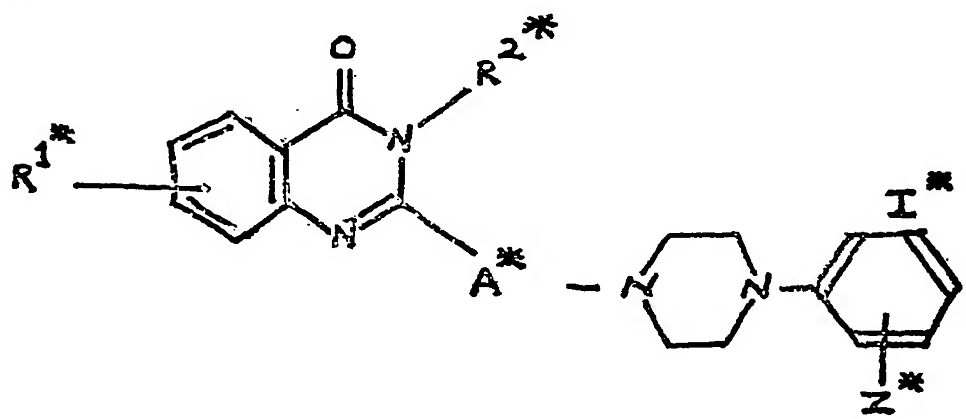


I

in which R¹ signifies a hydrogen atom, a halogen atom, one to three straight-chained or branched, alkyl groups with 1 to 6 carbon atoms or one to three straight-chained or branched, alkoxy groups with 1 to 6 carbon atoms,
R^2 signifies a hydrogen atom, a straight-chained or branched, alkyl group with 1 to 6 carbon atoms with 3 to 6 carbon atoms,
A signifies a straight-chained or branched, alkylene group with 1 to 6 carbon atoms,
Y signifies a hydrogen atom or an alkyl group with 1 to 4 carbon atoms and
Z signifies a hydrogen atom or one or more alkyl, alkoxy or alkylmercapto groups each with 1 to 4 carbon atoms, trifluoromethyl groups or fluorine, chlorine or bromine atoms.

2. Aryl-substituted piperazinylalkyl quinazolone-(4) derivatives of the general formula I given in Claim 1, and their salts with pharmacologically compatible inorganic or organic acids, in which R^1 is a hydrogen atom, a chlorine or bromine atom, 1 to 3 straight-chained or branched, alkyl groups with 1 to 6 carbon atoms or 1 to 3 straight-chained or branched alkoxy groups with 1 to 6 carbon atoms, and R^2, A, Y and Z have the meanings given in Claim 1.

3. Aryl-substituted piperazinyl quinazolone-(4) derivatives of the general formula I* and their salts with pharmacologically compatible inorganic or organic acids,



I*

in which R^{1*} signifies 1 to 2 methyl, ethyl, methoxy or ethoxy groups,
R^{2*} signifies a hydrogen atom, a methyl or ethyl group,
A* signifies an ethylene or trimethylene group, and
Z* signifies a fluorine or chlorine atom, a methyl or alkoxy group with 1 to 4 carbon atoms.

4. Aryl-substituted piperazinylalkyl quinazolone-(4) derivatives of the general formula I* given in Claim 3 and their salts with pharmacologically compatible inorganic or organic acids, in which R^{1*} signifies from 1 to 2 methyl, ethyl, methoxy or ethoxy groups in the 6 and/or 7 position, and R^{2*}, A* and Z* have the meanings given in Claim 3.